sequencing rather than amplification. Hosoi relies upon providing all possible primers of a given length, immobilizing these at predetermined regions so that each region contains only one type of primers, hybridizing the primers to a template, adding dNTPS and a polymerase and and determining the degree of primer extension (if any) occurring at each region. Hosoi requires many different types of primers. 3mers and 8mers are discussed (see page 5, lines 15 to 20, and page 11, lines 30 to 34, respectively). These require 4^3 (64) and 4^8 (65536) different types of primer, respectively.

A key advantage of Hosoi is indicated to be the use of "**single-stroke** picturing" in order to determine a sequence. This enables sequence information to be provided very rapidly (see e.g. page 3, line 47 to 50, and page 3, lines 24 to 25, of Hosoi). Thus, Hosoi leads away from repeated cycles of primer extension and sequencing. A non-inventive, skilled person would, therefore, not have considered modifying the teaching of Hosoi by introducing repeated PCR cycles.

It is also significant that Hosoi relies upon providing **only one type of primer** within each region and requires different regions to be spaced well apart in wells or other separate areas (see e.g Fig 1 of Hosoi). The

method of Hosoi would not work if different primers were allowed to be present together in a single region. In complete contrast, the present invention utilizes different primers within a single region in order to hybridize to different complementary sequences at the ends of molecules being amplified (see e.g. Fig 8 of the present application).

The Examiner has argued that it would have been obvious to modify the teaching of Hosoi by including the PCR step disclosed in Cheng, because PCR allows repeating cycles to be performed and can be utilized at temperatures at which the sequencing apparatus disclosed by Hosoi can be used (see the final sentence of page 7 of the Office Action). However there is an infinite number of procedures that **could** be carried out within the temperature range at which the appartus of Hosoi works. This would not have made it obvious to combine a particular procedure with the method of Hosoi. The key issue is not whether a non-inventive, skilled person **could** have combined a particular procedure with the Hosoi method, but whether it **would** have been obvious for such a person to have done so in the absence of hindsight analysis.

From the comments provided in the foregoing paragraphs it is clear that such a combination would not have been

obvious. However, even if it were to have been an obvious combination to make (which is denied) this would have neither resulted in the present invention, nor have rendered it obvious. As discussed in detail at pages 17 and 18 of the previous Amendment, Cheng does not teach performing amplification on a surface utilizing immobilized primers. On the contrary, Cheng is directed to providing a chip that reduces non-specific adsorption to the surface so that PCR occurs in a fluid environment (away from the surface).

The Examiner has argued that it would have been *prima facie* obvious to replace one solid support with another. However, given that Cheng is directed to **reducing** adsorption of PCR reagents to a surface so that PCR can occur in a fluid environment, it would not have been obvious to a non-inventive person to go in the opposite direction from Cheng and seek to attach PCR reagents to a surface. It should further be noted that the Examiner seems to have assumed that Cheng already provides a solid support for amplification and this could be modified in a particular manner. However, this is not correct. Cheng merely provides a reaction chamber in which standard PCR occurs in a fluid environment (see Figure 1 of Cheng).

This is, of course, completely different from the surface amplification method of the present invention.

The Examiner has discussed the need for an unexpected result if an invention is *prima facie* obvious. However, given that the present invention would not have been obvious for the reasons given above, an unexpected result is not required. Nevertheless, it is noted that, prior to the present invention, it was unexpected that the very high densities of immobilized molecules, achievable by the present invention, could be provided in such an elegant and effective manner and in discrete regions (see the discussion under the heading "Colonies" at pages 7 and 8 of the present application). This point is also relevant to the objection raised at page 8 of the Office Action that there is no invention involved in combining old elements. It is true that many of the individual steps of the present invention are known and with hindsight the invention may appear simple. However many important inventions are are patentable even though they are based upon combinations of known simple steps, because the particular combinations would have been non-obvious. A classic example of this is PCR. It has been explained in the foregoing paragraphs why the combination of steps used in the present invention would have been non-obvious. As with PCR, the non-obvious

combination of steps of the present invention provides major benefits in the field of nucleic acid amplification.

Reconsideration is requested.

Claims 19 and 20 stand rejected under 35 USC 103 as allegedly being obvious over Hosoi et al and Cheng et al and further in view of Hahn et al. The rejection is traversed.

The Examiner's attention is directed to the foregoing comments responsive to the rejection of the claims as obvious over Hosoi et al and Cheng et al. Those comments are equally applicable here.

Additionally it should be borne in mind that none of Hosoi, Cheng and Hahn teach performing amplification on a surface. Hosoi relates to sequencing using very large numbers of primers, Cheng relates to amplification in a fluid environment (using standard PCR) and specifically seeks to avoid adsorption of PCR reagants to a surface. Like Cheng, Hahn performs amplification in a fluid environment (using standard PCR with specific internal restriction sites). Although Hahn provides immobilized nucleic acid molecules, immobilization occurs only after amplification.

Thus, even if there had been good reason for a non-inventive, skilled person to combine Hosoi, Cheng and Hahn

(which is denied), then it is clear that the present invention would not have resulted.

A further point to note is that it is over-simplistic to argue that it would have been *prima facie* obvious to immobilize primers, perform amplification on and then use a restriction enzyme "as a nice way to release an immobilized nucleic acid" (the Examiner's phrase). If it were desired to provide large amounts of amplified, non-immobilized nucleic acid prior to the present invention, the obvious way to do this would have been to have used standard PCR. (Why go to the trouble of immobilizing primers at specific locations on a particular surface and then amplifying nucleic acids on the surface using the immobilized primers, only to cleave the immobilized nucleic acids later on?) It is therefore clear that the restriction enzyme cleavage step set out in Hahn is intended for the specific RED-ELISA scheme shown in Figure 2 of Hahn and would in no way have rendered claims 19 and 20 obvious.

Reconsideration is requested.

The following comments are offered with regard to the Examiner's "Response to Arguments" section.

The Examiner contends that the arguments relating to Hosoi based upon primer location are not relevant because the present claims do not limit the primers of the present

invention to being close to another. This is incorrect. Step D) of claim 1 makes it clear that, following hybridization, primer extension and separation, an extended primer must be sufficiently close to an adjacent primer to allow hybridization thereof (see also the figures of the present application).

The Examiner has argued that the comments made regarding the complexity of the plates required by Hosoi are not relevant. However, these comments are very relevant. They emphasise the completely different approach taken by Hosoi from that of the present invention and, therefore, provide evidence of non-obviousness. Hosoi teaches that primers with very many different sequences should be prepared and that each different type primer must be located at a discrete region. In contrast, the present invention requires far fewer primers (generally two will be used for each molecule to be amplified) and allows both forward and reverse primers to be present at a given region.

The comments provided in the previous Amendment in respect of immobilization, solid supports etc., are highly relevant in demonstrating non-obviousness. In the present Office Action, the Examiner has again raised objections of *prima facie* obviousnesss in respect of performing

amplification on solid supports. Applicants are entitled to explain why this is not the case and to refer to the documents cited by the Examiner to provide evidence of non-obviousness.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page/s is/are captioned "**Version With Markings To Show Changes Made**."

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Cancel claims 27-30 without prejudice.

62. (Twice Amended) An apparatus according to claim 61 wherein said detector means has sufficient resolution to distinguish between the distinct areas on a surface, each area comprising a plurality of identical nucleic acid strands and a plurality of identical complementary strands thereto; wherein each nucleic acid strand within such an area is located [so that another nucleic acid strand is located] on the surface within a distance of [the] its length [of that] from another strand.

Cancel claim 65 without prejudice.